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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,555	07/30/2003	Kohei Miyazono	NY-LUD 5298.5-DIV-US	7477

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,555	MIYAZONO ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. In the Applicant's letter received on 5/4/2006, the Applicant's point out that the requirement for restriction, mailed on 4/28/2006, required restriction among claims that had been previously cancelled in the preliminary amendment received on 7/30/2003. The preliminary amendment of 7/30/2003 had cancelled claims 1-31, which were the subject of the requirement for restriction, and added new claims 32-33.

2. Accordingly, the requirement for restriction, mailed on 4/28/2006, is hereby vacated.

3. Claims 32-33 are currently pending and are the subject of this Office Action.

Specification

The specification is objected to as being incomplete. Applicants should include updated bibliographic information in the first paragraph. Appropriate correction is required.

Claim Objections

1. The Examiner suggests the syntax of claim 32 can be improved by amending the phrase "active like" to "activin-like".

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 32-33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility. The claims are drawn to an isolated antibody that binds specifically to a human protein having

activin-like kinase activity which is encoded by a nucleic acid sequence, the complement of which hybridizes to the nucleotide sequence of SEQ ID NO: 1, and an isolated antibody that binds specifically to an epitope of SEQ ID NO: 2. The invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated nucleic acid (SEQ ID NO: 1) which encodes activin receptor-like kinase-1 (ALK-1, SEQ ID NO: 2). However, the instant application does not disclose a specific and substantial biological role of ALK-1 or its significance.

The Applicants have putatively identified the protein of their invention as an activin receptor-like kinase, which is a member of the TGF-β family (p. 3, lines 23-36). However, the instant application does not disclose the biological role of the claimed protein or its significance, and the basis that the receptor of the present invention is an activin receptor-like kinase is not predictive of a use. The specification does not disclose any function or disease state associated with altered levels of forms of the polynucleotide (SEQ ID NO: 1) or polypeptide (SEQ ID NO: 2) to which the claimed antibody binds. The Applicants have only based the function of the protein of the present invention on homology to other receptors. Therefore, the specific function of an antibody to this protein would be speculative and significant, further experimentation would be required of the skilled artisan to identify a dysfunction or disease that is associated with the polypeptide (SEQ ID NO: 2), to which the claimed antibody binds. There is no disclosure, for example, of any symptoms associated with a disease or function of this polypeptide.

The specification discloses that the protein of SEQ ID NO: 2 (ALK-1) has sequence similarity to known TGF-β family receptors (p. 4, lines 3-6 and Table II, p. 20). Based on the structural similarity, the specification asserts that the newly disclosed SEQ ID NO: 2 has a similar activity. The assertion that the disclosed proteins have biological activities similar to known TGF-β family receptors cannot be accepted in the absence of supporting evidence, because generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick *et al* (2000, *Trends in Biotech.* 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, *Genome Research* 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison

of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks *et al.* (1998, *Trends in Genetics* 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith *et al.* (1997, *Nature Biotechnology* 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene.

Brenner (1999, *Trends in Genetics* 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork *et al.* (1996, *Trends in Genetics* 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of antibodies to the protein of SEQ ID NO: 2, or encoded by the polynucleotide of SEQ ID NO: 1, wherein said protein is only known to be homologous to TGF-β family receptors. Thus, the instant claims are drawn to an antibody to a protein that has an undetermined function or biological significance. There is no actual and specific significance that can be attributed to said ALK-2 protein (SEQ ID NO: 2) identified in the specification. For this reason, the instant invention is incomplete. In the absence of knowledge of the biological significance of this protein, there is no immediately obvious patentable use for it. To employ the protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said ALK-1 is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Therefore, an antibody to a protein that has no utility would, itself, not possess utility. Since the instant specification does not disclose a "real-world" use for said ALK-1 protein, the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

The instant situation is directly analogous to that of which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form - there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

There is little doubt that, after complete characterization, this protein, and therefore, the claimed antibody, will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, the Applicants' claimed invention is incomplete.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 32-33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility. Therefore, claims 32-33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility, for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

2. Claims 32-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breath of claims. Ex Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claim 32 recites an antibody against a polypeptide encoded for by a polynucleotide which hybridizes to the nucleotide sequence of SEQ ID NO: 1, wherein the polypeptide has activin-like activity. The breadth of the claim is excessive with regards to claiming all possible antibodies against any and all possible polypeptides having an amino acid sequence encoded for by a polynucleotide which hybridizes to SEQ ID NO: 1 and which has activin-like activity. Proteins encoded for by polynucleotides which hybridize to SEQ ID NO: 1 could have one or more amino acid substitutions, deletions, insertions, and or additions to that encoded for by SEQ ID NO: 1. In addition, although the claim recites hybridization conditions, there are no wash conditions specified. Without a specific recitation of the wash conditions, a person of ordinary skill in the art would not be able to predict whether or not the recited hybridization conditions would be specific for only SEQ ID NO: 1. Furthermore, the limitation that the protein must have activin-like activity does not reasonably limit the scope of the claim. Binding to an antibody, for example, is an activin-like activity, and thus any antibody which binds any protein encoded for by a polynucleotide which hybridized to SEQ ID NO: 1 would meet the limitation of the claims. Therefore, the number of antibodies encompassed by the claims of the present invention would be excessive. The Applicants have not even demonstrated that they are in possession of an antibody which specifically binds a protein encoded for by SEQ ID NO: 1, or specifically to residues 145-166 of SEQ ID NO: 2 (i.e. binds to no other protein). Furthermore, the Applicants have not provided guidance or working examples of any antibodies to the protein encoded for by SEQ ID NO: 1, or to residues 145-166 of SEQ ID NO: 2, nor have they provided

any guidance or working examples of antibodies to polypeptides encoded for by polynucleotides which hybridize to SEQ ID NO: 1.

In summary, even if the antibody of the present invention possessed utility under 35 U.S.C. 101, the Applicants would still not be enabled for antibodies which specifically bind proteins encoded for by polynucleotides which hybridize to SEQ ID NO: 1, or which bind residues 145-166 of SEQ ID NO: 2, nor for the excessive breadth of antibodies to any and all polypeptides encoded for by polynucleotides which hybridize to SEQ ID NO: 1. There is also a lack of guidance and working examples of these proteins and antibodies. Therefore, a person of ordinary skill in the art would require further, undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 32-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention.

This rejection can be viewed as a genus of either the protein (and the encoding polynucleotides), or of the antibodies that bind the protein. However, to make the rejection clear, the Examiner feels that the best way to describe the lack of written description of the genus of antibodies is to describe the lack of written description for the genus of proteins (and encoding polynucleotides) to which the claimed genus of antibodies bind. The claims recite antibodies against a polypeptide having an amino acid sequence encoded for by a polynucleotide which hybridizes to SEQ ID NO: 1. These proteins could have one or more amino acid substitutions, deletions, insertions, and/or additions to said proteins.

The specification and claims do not indicate what distinguishing attributes are shared by the members of this genus of proteins to which the claimed antibodies bind, other than that the protein must have activin-like activity. Thus, the scope of the claims includes numerous structural variants, and the genus of proteins is highly variant because a significant number of structural differences between genus members would be expected. The specification and claims do not provide any guidance as to what changes should be made to these proteins. Structural features that could distinguish compounds in the genus from others in the protein

class are missing from the disclosure, and no common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Because the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 1, or antibodies to proteins encoded by polynucleotides that hybridize to SEQ ID NO: 1, alone are insufficient to describe the genus.

The specification only provides a written description of SEQ ID NO: 1, and contemplates an antibody to the protein encoded by a polynucleotide that hybridizes to SEQ ID NO: 1. No other species of protein are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict critical amino acid residues that would structurally characterize the genus of proteins, other than that encoded by SEQ ID NO: 1, because it is unknown and not described what structurally constitutes any different proteins, other than that encoded for by SEQ ID NO: 1; thereby not meeting the written description requirement under 35 U.S.C. 112, first paragraph. One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus of proteins, and therefore, antibodies that bind these proteins. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 32-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite a human protein having "activin like" kinase activity. The metes and bounds of the term "activin like" are not clear, and thus the claim is indefinite. Claim 33 is rejected for depending from rejection claim 32.

2. Claims 32-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The claims recite hybridization conditions, followed by two 15 minutes washes. The wash conditions (temperature, SSC and SDS concentrations, etc) are not defined by the claim, and therefore the claim is indefinite. Claim 33 is rejected for depending from rejected claim 32.

3. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to an isolated antibody that binds specifically to an epitope *by* amino acids 145-166 of SEQ ID NO: 2. The metes and bounds of the phrase "by amino acids....." are not defined. It is not clear whether the antibody is intended to bind within the region of amino acids 145-166 of SEQ ID NO: 2, or an epitope that is somewhere adjacent to this region, and if so, how far from amino acids 145-166?

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claim 32 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. 6,692,925. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 3 of the

'925 patent is drawn to an antibody that binds the extracellular domain of ALK-1. The specification of the instant specification teaches that ALK-1 is encoded by the polynucleotide of SEQ ID NO:1. Claim 32 of the instant application is drawn to an antibody that specifically binds any protein encoded by a nucleotide sequence, the complement of which hybridizes to SEQ ID NO: 1. It would be obvious to one of ordinary skill in the art, therefore, that the antibody of claim 3 of the '925 application would meet the limitations of claim 32 of the instant application.

2. Claim 32 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,982,319. Although the conflicting claims are not identical, they are not patentably distinct from each other because, as stated in the 35 U.S.C. 112, first paragraph enablement rejection above, the claim is drawn to any antibody that recognizes a protein encoded by a nucleic acid capable of hybridizing to SEQ ID NO: 1. Claim 1 of the '319 patent is drawn to an antibody that specifically binds to a protein encoded by a nucleic acid, the complement of which hybridizes to SEQ ID NO: 9, which is disclosed to be ALK-5. Figure 3 of the instant application shows that ALK-1 and ALK-5 share regions of extensive homology, such as the high homology seen in domains IV, VB, and VIII. Therefore, one of ordinary skill in the art could reasonably conclude that an anti-ALK5 antibody that binds specifically to one of these domains would also have binding affinity for the same domain of ALK-1, and thus meet the limitations of claim 32 of the instant application.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH
Art Unit 1646

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